Identification of FOXM1 as a therapeutic target in B-cell lineage acute lymphoblastic leukaemia.

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Public Summary:
Despite recent advances in the cure rate of acute lymphoblastic leukaemia (ALL), the prognosis for patients with relapsed ALL remains poor. Here we identify FOXM1 as a candidate responsible for an aggressive clinical course. We show that FOXM1 levels peak at the pre-B-cell receptor checkpoint but are dispensable for normal B-cell development. Compared with normal B-cell populations, FOXM1 levels are 2- to 60-fold higher in ALL cells and are predictive of poor outcome in ALL patients. FOXM1 is negatively regulated by FOXO3A, supports cell survival, drug resistance, colony formation and proliferation in vitro, and promotes leukemogenesis in vivo. Two complementary approaches of pharmacological FOXM1 inhibition-(i) FOXM1 transcriptional inactivation using the thiazole antibiotic thiostrepton and (ii) an FOXM1 inhibiting ARF-derived peptide-recapitulate the findings of genetic FOXM1 deletion. Taken together, our data identify FOXM1 as a novel therapeutic target, and demonstrate feasibility of FOXM1 inhibition in ALL.

Scientific Abstract:
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